16. (Twice amended) A method for treating a medical condition of the type that is characterized by the destruction of articular cartilage; wherein said medical condition comprises joint injury, reactive arthritis, acute pyrophosphate arthritis (pseudogout), psoriatic arthritis, osteoarthritis or juvenile rheumatoid arthritis; in a mammalian subject, which method comprises administering to the subject having said condition a therapeutically effective amount of a small molecule having a molecular weight of under 2000 grams/mole, wherein the small molecule exhibits an aggrecanase IC_{50} of less than about 20 nM, said aggrecanase IC_{50} measured by an aggrecanase chondrocyte assay.

REMARKS

Reconsideration of the above application is respectfully requested.

Claims 1-23 are pending in the application. Claims 1-15 and 21-23 have been withdrawn from consideration as directed to non-elected subject matter. By this Amendment Applicants have, hereinabove, amended claim 16. Upon entry of this amendment, claims 16-20 are pending. Entry of this amendment is respectfully requested.

I. 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 16-20 under 35 U.S.C. § 112, First Paragraph on the grounds that claims 16-20, while being enabling for small molecules of the formula I, do not reasonably provide enablement for all small molecules. Applicants traverse the Examiner's rejection on the grounds that the Examiner's rejection is improper as a matter of law.

Applicants respectfully traverse the Examiner's enablement rejection on the grounds that the specification as filed complies with the enablement requirement. Section 112 requires that a specification contain a written description of the manner and process of making and using the invention in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same. In accordance with the statute, the specification of the instant application fully supports and enables the pending claims. The test of enablement is whether one skilled in the art could make or use the invention relying on the disclosure in the patent coupled with information known in the art without undue experimentation. U.S. v. Telectronics, Inc. 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); M.P.E.P. § 2164.01. Applicant also submits that statements in the specification are to be accepted as presumptively true, In re Brana, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Applicants have submitted an enabling disclosure including the use of exemplified compounds that are believed to be the best mode, see pages 65-82 of the specification as originally filed. Applicants have also described multiple schemes of preparation and starting materials that could be used by one skilled in the art to prepare the small molecules, see pages 22-51 of the specification, Schemes 1-7 and their descriptions. Applicants have stated throughout the specification that their invention is useful for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject. See

for example the specification page 13, lines 19-30. Applicants have also described several aggrecanase and TACE assays (pages 51-55), which demonstrate the utility of the claimed compounds. Applicants have also provided the exemplified activity data of the claimed compounds against collagenase-1 (see page 51), against collagenase-3 (see page 52), against aggrecanase (see page 53), and against TACE (see page 55). Applicants have further provided comparative data in Table 2 on pages 56-63 of the specification, which shows activities data for many preferred small molecules, including the preferred hydroxamic acids, against aggrecanase, MMP-13, MMP-1 and TACE. Applicants have also provided a detailed description of methods for dosing and formulating the compounds of the invention, see pages 63-64. The Examiner has not challenged Applicant's disclosure on any of these points. Instead, the Examiner has, without any factually supported evidence, concluded that Applicants' broad claims lack sufficient supporting description (i.e., what chemical structures and how to make such compounds, see office action page 3, middle of page). Such factually unsupported evidence argued in the absence of the specification disclosure and cited literature is contrary to Patent Office standards and Applicant objects to such improper line of analysis, see M.P.E.P. 2164.01(a), which states:

> It is improper to conclude that a disclosure is not enabling based on analysis of only one of the above factors while ignoring one or more of the others. The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusions of non-enablement must be based on the evidence as a whole. 858 F.2d at 737, 740, 8 U.S.P.Q.2d at 1404, 1407.

The Examiner's obligation is clearly to ground his reasoning in factual evidence, see M.P.E.P. 2164.04, which states:

> As stated by the court, "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."... This can be done by making specific findings of facts, supported by the evidence, and then drawing conclusions based on these findings of fact (emphasis added).

The Examiner has cited In re Fisher, 166 U.S.P.Q. 18, in concluding that the present claims 16-20 are not enabled. Applicants extend their appreciation of the Examiner's effort to conduct a legal research for enablement. In re Fisher cited by the Examiner describes a situation where an applicant for a patent disclosed the preparation of adrenocorticotrophic hormone (ACTH) to a potency of between 1. 11 and 2.30 International Units of ACTH activity per milligram of tissue extract, such preparation being useful in the treatment of arthritis and

other conditions. This level of potency was significantly higher than that achieved in prior art preparations of ACTH (emphasis added). The applicant in that case attempted to claim an ACTH preparation having a potency of "at least 1 International Unit of ACTH per milligram." Thus, using an open-ended claim language "at least," the applicant in that case attempted to claim his preparation more broadly than the specific embodiments disclosed in his specification. Id. at 839,166 U.S.P.Q. at 23,

The issue before the court in In re Fisher was whether the applicant in that case "should be allowed to dominate all such compositions having potencies greater than 1.0, including future compositions having potencies far in excess of those obtainable from [applicant's] teachings plus ordinary skill." Id. at 839,166 U.S.P.Q. at 24 (emphasis in original).

The court held as follows.

> It is apparent that such an inventor should be allowed to dominate the future patentable inventions of others where those inventions were based in some way on his teachings. Such improvements, while unobvious from his teachings, are still within his contribution, since the improvement was made possible by his work. It is equally apparent, however, that he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. 112. That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

The Fisher court thus concluded that while the applicant's disclosure provided one of ordinary skill in the art with sufficient guidance to prepare ACTH having certain potencies greater than 1 International Unit per milligram, it did not provide the requisite guidance for all potencies greater than 1. Accordingly, the claims were held unpatentable under § 112, first paragraph, because they did not "bear a reasonable correlation to" the scope of disclosure provided.

Applicants respectfully submit that unlike the claims in the Fisher case which call for a level of potency which is significantly higher than that achieved in prior art preparations of ACTH, the present claims call for a small molecule having a molecular weight of under 2000 grams/mole, which are obtainable from applicants' teachings plus ordinary skill. In contrast to the low level of ordinary skill in the preparations of ACTH art applicable to Fisher, the ordinary skill of the preparation and use of variety of small molecules for treating a medical condition of the type that is characterized by the destruction of articular cartilage is high. Among others, below are specific patent numbers, in United States alone, that are associated with small molecules, including hydroxamic derivatives, that are useful for treating a medical condition of the type that is characterized by the destruction of articular cartilage:

U.S. Patent No. 6,326,516, entitled "Acetylenic β-sulfonamido and phosphinic acid amide hydroxamic acid TACE inhibitors";

U.S. Patent No. 6,313,123, entitled "Acetylenic sulfonamide thiol TACE inhibitors;

U.S. Patent No. 6,277,885, entitled "Acetylenic aryl sulfonamide and phosphinic acid amide hydroxamic acid TACE inhibitors;

U.S. Patent No. 6,225,314, entitled "Inhibition of matrix metalloproteases by substituted biaryl oxobutyric acids;

U.S. Patent No. 6,225,311, entitled "Acetylenic α-amino acid-based sulfonamide hydroxamic acid TACE inhibitors;

U.S. Patent No. 6,200,996, entitled "Heteroaryl acetylenic sulfonamide and phosphinic acid amide hydroxamic acid TACE inhibitors;

U.S. Patent No. 6,197,795, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;

U.S. Patent No. 6,162,821, entitled "Preparation and use of ortho-sulfonamide heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;

U.S. Patent No. 6,162,814, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metaloproteinase and TACE inhibitors;

U.S. Patent No. 5,977,408, entitled "Preparation and use of β-sulfonamido hydroxamic acids as matrix metalloproteinase and TACE inhibitors;

U.S. Patent No. 5,968,795, entitled "Biaryl acetylenes as inhibitors of matrix metalloproteases;

U.S. Patent No. 5,962,481, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;

U.S. Patent No. 5,932,763, entitled "Inhibition of matrix metalloproteases by 2-(.omega.-arolalkyl)-4-biaryl-4-oxobutyric acids;

U.S. Patent No. 5,929,097, entitled "Preparation and use of ortho-sulfonamido aryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;

U.S. Patent No. 5,925,637, entitled "Inhibition of matrix metalloproteases by substituted biaryl oxobutyric acids;

U.S. Patent No. 5,804,581, entitled "Inhibition of matrix metalloproteases by substituted phenalkyl compounds; and

U.S. Patent No. 5,677,282, entitled "Amino acid amides of 1,3,4-thiadiazoles as matrix metalloproteinase.

Thus, Applicants respectfully submit that based on Applicants' teachings in addition to the high ordinary skill level described above, small molecules having a molecular weight of under 2000 grams/mole are obtainable. Therefore the present claims are enabled.

Furthermore, as described herein below, Applicant cites in re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982), and provides a rebuttal.

Applicants in in re Strahilevitz sought to broadly claim a method and devices for removing haptens, antigens, and antibodies from blood. Applicants in that case had described the invention with specificity, but had not disclosed even a single operative embodiment. The court acknowledged that the claims at issue were extremely broad. Yet the court reversed the Board's holding of non-enablement. Pointing out that § 112 does not require working examples, the court found the broad claims enabled throughout their scope.

As the decision in Strahilevitz amply illustrates, the decision in Fisher does not necessarily limit an applicant's claim scope only to those embodiments actually disclosed in the specification. One can support broad claims without even a single disclosed embodiment. See Spectra-Physics Inc. v. Coherent Inc., 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987); see also Utter v. Hiraga. 845 F.2d at 998, 6 U.S.P.Q.2d at 1714 (A specification may, within the

meaning of 35 U.S.C. § 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that claim encompasses), and the embodiment need not necessarily have even been reduced to practice. See In re Wright, 999 F.2d 1557,1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993) ("Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples.*); In re Robins, 429 F.2d 452,457,166 U.S.P.Q. 552,555 (C.C.P.A. 1970) (stating that representative [samples] are not required by the statute and are not an end in themselves"); In re Long, 368 F.2d 892, 895, 151 U.S.P.Q. 640, 642 (C.C.P.A, 1966) (holding that the absence of a working example does not in and of itself compel the conclusion that a specification does not satisfy the requirements of section 112).

Fisher and Strahilevitz thus illustrate, at opposite ends of the enablement spectrum, the basic precept in patent low that the requirements of § 112 are satisfied only if the disclosure reasonably apprises the ordinary artisan, in light of what is well-known in the art, how to make and how to use a claimed invention throughout its scope. Fisher is distinguished from Strahilevitz in the level and quality of disclosure that will suffice to enable the ordinary artisan to practice a claimed invention throughout its scope. The courts have pointed out that

> "[n]ot every last detail [of an invention need] be described [in a patent specification], else patent specifications would turn into production specifications, which they were never intended to be." In re Gay, 309 F.2d 769, 774, 135 U.S.P.Q. 311, 316 (C.C.P.A. 1962). Citing the opinion in Gay, the Board of Patent Appeals and Interferences echoed this point in its statement that 1he law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. 112, first paragraph," Staehelin v. Secher, 24 U.S.P.Q.2d 1513,1516 (Bd. Pat. App. & Int, 1992). Indeed, a specification need not describe-and best omits-that which is well-known in the art. See, e.g., In re Buchner, 929 F1d 660,661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991).

Based on the above legal precedents, the numerous examples of small molecules provided by Applicants, the breadth and depth of the level of the ordinary skill, and the copious number of small molecules in the art related to those in the present application, Applicants respectfully submit that they have put the public in possession of the claimed invention. Applicants have therefore provided more than sufficient basis for one of ordinary skill in the art to practice the teaching of the specification.

II. 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 16-20 as being indefinite to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The phrase "a medical condition of the type that is characterized by the destruction of articular cartilage"

First, the Examiner has asserted that the phrase "a medical condition of the type that is characterized by the destruction of articular cartilage" is indefinite. The Examiner asserts that the

claims do not set forth any steps involved in determining how to identify "a medical condition of the type that is characterized by the destruction of articular cartilage". The Examiner also asserts that it is unclear what diseases and treatments the Applicants intend to encompass. The Examiner has suggested that amending the claims to recite the specific diseases which Applicants list on page 4, lines 2-4, of the amendment dated 5/21/2001 [i.e., joint injury, reactive arthritis, acute pyrophosphate arthritis (pseudogout), psoriatic arthritis, osteoarthritis or juvenile rheumatoid arthritis] would overcome the rejection (see Office Action, page 7, last paragraph). Applicants have, hereinabove, amended claim 16 to include such diseases and thereby overcoming the indefiniteness rejection. Support for this amendment can be found throughout the specification as filed, *inter alia*, on page 8, lines 21-28; page 9, lines 7-11; page 10, lines 27-31; page 12, lines 5-9; page 13, lines 19-23; page 14, lines 35 to page 15, line 2; and page 63, lines 14-19. Applicants respectfully request that the Examiner remove his rejection on this ground.

The phrase "small molecules having a molecular weight of under 2000 grams/mole"

Second, the Examiner has asserted that the phrase "small molecules having a molecular weight of under 2000 grams/mole" is indefinite. The Examiner has asked Applicants tor the claimed chemical formulas. Applicants respectfully traverse the Examiner's indefiniteness rejection.

In the previous Office Action mailed January 23, 2001, the Examiner has stated that "claims 16-20 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. § 112, Second Paragraph, set forth in that Office Action" (see previous Office Action, page 6, paragraph 8). Specifically, in the previous Office Action, the Examiner has rejected Claims 16-20 on the grounds that the phrase "a small molecule" called for in these claims is allegedly indefinite. The Examiner requested that the molecular size be determined by volume, length, atomic number of constituent, or complexity. In the present Office Action, the Examiner has withdrawn the indefiniteness rejection because Applicants have amended claim 16 to recite "a small molecule with a molecular weight of under 2000 grams/mole". However, in the present Office Action, the Examiner has concluded that "the Examiner' analysis of the present claims as means plus function language interpreted according to 35 U.S.C. § 112, sixth paragraph and thus, reading upon only the specific species present in the application is erroneous." The Examiner states that "Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise." (See previous Office Action, page 2, paragraph 1). Applicants respectfully traverse the Examiner's rejection under 35 U.S.C. § 112, sixth paragraph because the phrase recite "a small molecule with a molecular weight of under 2000 grams/mole" is not a means-plus-function phrase and is definite as written.

35 U.S.C § 112, sixth paragraph, applies to claims written in means-plus-function format. Use of the phrase, "means for" or "step for" triggers a presumption that the drafter intended for § 112, sixth paragraph, to apply. Likewise, failure to use the word "means" in a claim element created a rebuttable presumption that § 112, sixth paragraph did not apply.

Personalized Media Communications, LLC v. Int'l Trade Comm'n, 161 F.3d 696, 703-04, U.S.P.Q.2d 1880, 1886-87 (Fed. Cir. 1998). See also *Rodime PLC v. Seagate Tech., Inc.,* 174 F.3d 1294, 1302, 50 U.S.P.Q.2d 1429, 1434 (Fed. Cir. 1999). This presumption is overcome if the claim itself recites sufficient structure or material for performing the claimed function or when it fails to recite a function associated with the means. See *Sage Prods., Inc. v. Devon Indus., Inc.,* 126 F.3d 1420, 1427-28, 44 U.S.P.Q.2d 1103, 1109 (Fed. Cir. 1997); *York Prods., Inc. v. Central Tractor Farm & Family Ctr.,* 99 F.3d 1568, 1574, 40 U.S.P.Q.2d 1619, 1623 (Fed. Cir. 1996).

Applicants fail to see the Examiner's ground of new rejection and respectfully request clarification. Nevertheless, the Examiner's attention is directed to the language of claims 16-20, i.e., which recites recite "a small molecule with a molecular weight of under 2000 grams/mole, wherein the small molecule exhibits an aggrecanase IC_{50} of less than about 20 nM, said aggrecanase IC_{50} measured by an aggrecanase chondrocyte assay." Applicants respectfully submit that the scope of the claim as written is very definite because the small molecule is defined both by its molecular weight (under 2000 grams/mole) and its feature (an aggrecanase IC_{50} of less than about 20 nM). Applicants submit that the Examiner's assertion that there is infinite number of a small molecule with a molecular weight of under 2000 grams/mole is incomplete as the claim calls for not only small molecules having a defined molecular weight but also a feature of aggrecanase IC_{50} of less than about 20 nM.

Applicants submit that the specification has provided ample support (aggrecanase assays, synthesis of the exemplified small molecules, and activity data against aggrecanase, as described above) for this claim requirement. Applicants therefore request that the Examiner remove the new grounds of rejection.

For the above reasons Applicants respectfully submit that claims 16-20 satisfy 35 U.S.C. §112, second paragraph, and Applicants request that the Examiner remove her rejection on this ground.

III. 35 U.S.C. § 102(e)

The Examiner has rejected claims 16-20 under 35 U.S.C. §102(e) as being anticipated by Robinson (U.S. Patent No. 6,114,361); Reiter (U.S. Patent No. 6,087,392); and Duan (U.S. Patent No. 6,057,336).

Applicants respectfully traverse the Examiner's rejections on the grounds that the present claims 16-20 call for a small molecule that exhibits an aggrecanase IC_{50} of less than about 20 nM. This requirement is not present anywhere in any of the above references cited by the Examiner. To anticipate a claim, a single source must contain all of the elements of the claim. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.,* 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984); *In re Marshall,* 578 F.2d 301, 304, 198 U.S.P.Q.

344, 346 (C.C.P.A. 1978). Missing elements may not be supplied by the knowledge of one skilled on the art or the disclosure of another reference. See *Structural Rubber Prods. Co. v. Park Rubber Co.,* 749 F.2d 707, 716, 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984). However, the prior art reference is not limited to its examples or its claims; the entire reference may be reviewed for an anticipatory disclosure. See *Palackal v. Resconi,* 2000 Pat. App. LEXIS 1, *54 (Bd. Pat. App. & Int. 2000)(non-precedential) citing *In re Mills*, 470 F.2d 649, 651, 176 U.S.P.Q. 196, 198 (C.C.P.A. 1972).

Applicants respectfully submit that the intended property of the claimed small molecules, *i.e.*, those having aggrecanase IC_{50} of less than about 20 nM is distinguishable from the cited references. Where the claim terms recite a property or intended use distinguishable from the prior art, an anticipation rejection may not be appropriate. See *E.I. Du Pont de Nemours & Co. V. Phillips Petroleum Co.,* 849 F.2d 1430, 1435, 7 U.S.P.Q.2d 1129, 1133 (Fed. Cir.I 1988), noting that "[o]n occasion, particularly with polymers, structure alone may be inadequate to define the invention, making it appropriate to define the invention in part by property limitations". Applicants' traversal is as follows:

Robinson (U.S. Patent No. 6,114,361, hereinafter '361)

The Examiner states that claims 16-20 are anticipated by '361 because the passage spanning line 66 of column 1 to line 6 of column 2 of '361 teaches aggrecanase inhibitory activity. The Examiner also states that claim 15 of '361 lists treatment of specific diseases, which include Applicants' limitation "destruction of articular cartilage". Applicants respectfully traverse.

Reference '361 is directed to 5-oxo-pyrrolidine-2-carboxylic acid hydroxamide derivatives that are inhibitors of zinc metalloendopeptidases, especially those belonging to the matrix metalloproteinase (also called MMP or matrixin) and reprolysin (also known as adamylsin) subfamilies of the metzincins (see '361, col. 1, lines 13-17). Select compounds of the '361 are potent inhibitors of aggrecanase, an enzyme important in the degradation of cartilage aggrecan. Aggrecanase is also believed to be an ADAM. The loss of aggrecan from the cartilage matrix is an important factor in the progression of joint diseases such as osteoarthritis and rheumatoid arthritis and inhibition of aggrecanase is expected to slow or block the loss of cartilage in these diseases. (see '361, col. 1, line 64, to col. 2, line 6). '361 provides an aggrecanase assay (see '361, col. 21, line 25, to col. 22, line 12, as pointed out by the Examiner). However, nowhere in '361 is an aggrecanase inhibition IC_{50} of less than about 20 nM stated. In contrast, the present Applicants have provided throughout the specification this important distinguishing feature of aggrecanase IC_{50} of less than about 20 nM, *inter alia*, at page 13, lines 15-30. Further, the present Applicants have provided *in vitro* data (see, *inter alia,* pages 56-63, Table 2) showing that the preferred compounds have aggrecanase IC_{50} of less

than about 20 nM, *i.e.,* 24 of the compounds in Table 2 have either ++ or + activities against aggrecanase, which refer to at least aggrecanase IC_{50} of less than about 20 nM. Applicants respectfully submit that the distinguishing feature of aggrecanase IC_{50} of less than about 20 nM called for in claims 16-20 is not contemplated within '361 and therefore claims 16-20 cannot be anticipated by '361. Withdrawal of this rejection is requested.

Reiter (U.S. Patent No. 6,087,392, hereinafter '392)

The Examiner states that claims 16-20 are anticipated by '392 because lines 1-8 of column 1 of '392 teaches aggrecanase inhibitory activity. The Examiner also states that claim 7 of '392 lists treatment of specific diseases, which include Applicants' limitation "destruction of articular cartilage". Applicants respectfully traverse.

Reference '392 is directed to (4-arylsulfonylamino)-tetrahydropyran-4-carboxylic acid hydroxamides that are inhibitors of zinc metalloendopeptidases, especially those belonging to the matrix metalloproteinase (also called MMP or matrixin) and reprolysin (also known as adamylsin) subfamilies of the metzincins (See '392, col. 1, lines 16-19). Select compounds of the '392 are potent inhibitors of aggrecanase, an enzyme important in the degradation of cartilage aggrecan. Aggrecanase is also believed to be an ADAM. The loss of aggrecan from the cartilage matrix is an important factor in the progression of joint diseases such as osteoarthritis and rheumatoid arthritis and inhibition of aggrecanase is expected to slow or block the loss of cartilage in these diseases. (See '392, col. 2, lines 1-8). '392 provides an aggrecanase assay (See '392, col. 16, lines 28-36). However, nowhere in '392 is the aggrecanase IC_{50} of less than about 20 nM stated. In contrast, as discussed above in the traversal of the Examiner's rejection over reference '361, the present Applicants have provided throughout the specification this important distinguishing feature of aggrecanase IC_{50} of less than about 20 nM and *in vitro* data showing the same. Applicants respectfully submit that the distinguishing feature of aggrecanase IC_{50} of less than about 20 nM called for in claims 16-20 is not contemplated within '361 and therefore claims 16-20 cannot be anticipated by '361. Withdrawal of this rejection is requested.

Duan (U.S. Patent No. 6,057,336, hereinafter '336)

The Examiner states that claims 16-20 are anticipated by '336 because lines 43-46 of column 238 of '336 teaches aggrecanase inhibitory activity. The Examiner also states that claims 9-12 of '336 list treatment of specific diseases, which include Applicants' limitation "destruction of articular cartilage". Applicants respectfully traverse.

Reference '336 is directed to lactam metalloprotease inhibitors (see '336, col. 1, lines 8-10). The '336 lactam compounds are expected to have the ability to suppress/inhibit cartilage degradation in vivo, for example, as demonstrated using the animal model of acute cartilage

degradation described in aggrecanase assay (see '336, col. 238, lines 43-46, as pointed out by the Examiner). The kinetic studies using this assay yield a Km of 1.5+/-0.35 μM for aggrecanase (see '336, col. 238, lines 35-36). Nowhere in '336 the aggrecanase IC_{50} of less than about 20 nM is stated. A Km of 1.5+/-0.35 μM is about 75 times less active than about 20 nM. As discussed above in the traversal of the Examiner's rejection over references '361 and '392, the present Applicants have provided throughout the specification this important distinguishing feature of aggrecanase IC_{50} of less than about 20 nM and *in vitro* data showing the same. Applicants respectfully submit that the distinguishing feature of aggrecanase IC_{50} of less than about 20 nM called for in claims 16-20 is not contemplated within '336 and therefore claims 16-20 cannot be anticipated by '336. Withdrawal of this rejection is requested.

IV. Conclusion

In light of the above arguments, legal precedents, and claim amendment, Applicants submit that pending claims 16-20 are patentable, and respectfully request that they be allowed to issue.

Respectfully submitted,

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